

General

Guideline Title

Guideline for the prevention and treatment of anticipatory nausea and vomiting due to chemotherapy in pediatric cancer patients.

Bibliographic Source(s)

Dupuis LL, Robinson PD, Boodhan S, Holdsworth M, Portwine C, Gibson P, Phillips R, Maan C, Stefin N, Sung L. Guideline for the prevention and treatment of anticipatory nausea and vomiting due to chemotherapy in pediatric cancer patients. Toronto (ON): Pediatric Oncology Group of Ontario (POGO); 2014 Apr 23. 57 p. [99 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [December 14, 2016 – General anesthetic and sedation drugs](#) : The U.S. Food and Drug Administration (FDA) is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains. Consistent with animal studies, recent human studies suggest that a single, relatively short exposure to general anesthetic and sedation drugs in infants or toddlers is unlikely to have negative effects on behavior or learning. However, further research is needed to fully characterize how early life anesthetic exposure affects children's brain development.
- [August 31, 2016 – Opioid pain and cough medicines combined with benzodiazepines](#) : A U.S. Food and Drug Administration (FDA) review has found that the growing combined use of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. FDA is adding Boxed Warnings to the drug labeling of prescription opioid pain and prescription opioid cough medicines and benzodiazepines.

Recommendations

Major Recommendations

Strength of recommendations (Strong, Weak) and quality of evidence (High, Moderate, Low, Very Low) are defined at the end of the "Major Recommendations" field.

Health Question #1: What approaches are recommended to prevent the development of anticipatory chemotherapy-induced nausea and vomiting (CINV) in children?

Recommendation

Control of acute and delayed CINV should be optimized for each child in order to minimize the risk of the child developing anticipatory CINV. (Strong Recommendation, Low Quality Evidence)

Health Question #2: What interventions are recommended to control anticipatory CINV in children who develop it?

Recommendations

- The panel suggests that psychological interventions such as hypnosis or systematic desensitization may be offered to children with anticipatory CINV. (Weak Recommendation, Moderate Quality Evidence)
- The panel suggests that lorazepam in a dose of 0.04 to 0.08 mg/kg/dose (maximum 2 mg/dose) once at bedtime the night before chemotherapy and once the next day prior to administration of chemotherapy may be used to prevent or treat anticipatory CINV in children. (Weak Recommendation, Low Quality of Evidence)

Definitions:

Quality of Evidence

High Quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate Quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low Quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low Quality	Any estimate of effect is very uncertain

Strength of Recommendations

Strong Recommendation	When using Grading of Recommendations Assessment, Development and Evaluation (GRADE), panels make strong recommendations when they are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
Weak Recommendation	Weak recommendations indicate that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Anticipatory chemotherapy-induced nausea and vomiting (CINV)

Guideline Category

Management

Prevention

Treatment

Clinical Specialty

Nursing

Oncology

Pediatrics

Preventive Medicine

Intended Users

Advanced Practice Nurses

Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To optimize the control of anticipatory chemotherapy-induced nausea and vomiting (CINV) in children receiving chemotherapy

Note: For the purpose of this guideline, optimal anticipatory CINV control is defined as no vomiting, no retching, no nausea, no use of antiemetic agents other than those given for anticipatory CINV prevention or treatment and no nausea-related change in the child's usual appetite and diet. This level of CINV control is to be achieved during the 24 hours prior to administration of the first antineoplastic agent of the upcoming chemotherapy block.

Target Population

Children (0 to 18 years) receiving chemotherapy for cancer and who are at risk of experiencing anticipatory chemotherapy-induced nausea and vomiting (CINV)

Interventions and Practices Considered

1. Optimization of control of acute and delayed chemotherapy-induced nausea and vomiting (CINV)
2. Psychological interventions such as hypnosis or systematic desensitization
3. Lorazepam

Major Outcomes Considered

- Prevalence of and risk factors for chemotherapy-induced nausea and vomiting (CINV)
- Proportion of patients with complete control of anticipatory CINV

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Identification and Appraisal of Existing Guidelines

A guideline was sought which could be adapted to the Pediatric Oncology Group of Ontario (POGO) context for the management of anticipatory chemotherapy-induced nausea and vomiting (CINV).

- a. **Guideline Search Strategy:** During August and September 2012, the POGO CINV Guideline Development Group conducted a search of bibliographic databases and the grey literature to identify existing practice guidelines for the management of anticipatory CINV in children with cancer. Computerized searches were performed with the assistance of a library scientist using the OVID search platform for the MEDLINE and EMBASE databases. The search engine Google was utilized for identification of grey literature including local, provincial, national and international databases. In addition the panel members reviewed their files for potentially relevant guidelines. The search strategies are provided in Appendix A in the original guideline document.
- b. **Guideline Selection Criteria and Appraisal:** Guidelines were selected for inclusion that: (i) provided recommendations for the management of anticipatory, breakthrough and/or delayed CINV; (ii) were published in 2008 or more recently; and (iii) were published in English. Financial limitations precluded translation of guidelines published in languages other than English. Guidelines were excluded if it was not clear that the guideline statements or recommendations were based on a review of evidence from the literature and/or were not based on a source that used evidence to support the guideline development process.

Systematic Reviews of Primary Studies

- a. **Prevention and Treatment of Anticipatory CINV:** As none of the guidelines identified specifically addressed the management of anticipatory CINV in children with cancer and there was variability between the adult-focused guidelines on inclusion of studies addressing anticipatory CINV, a systematic review of primary studies evaluating anticipatory CINV in adults and/or children was conducted.
 - i. **Search Strategy:** The following databases were searched and included articles indexed as of November 28, 2012: OvidSP - MEDLINE, EMBASE & EMBASE Classic, EBM Reviews – Cochrane Central Register of Controlled Trials (CCTR), HaPI (Health and Psychosocial Instruments), AMED (Allied and Complementary Medicine); EBSCOHost CINAHL; ProQuest Dissertation Abstracts. The search strategies are provided in Appendix C in the original guideline document.
 - ii. **Selection Criteria and Appraisal:** Citations were independently screened for relevancy by two reviewers. All citations identified as potentially relevant by either reviewer were included for full-text screening. Two reviewers independently evaluated the full-text papers to determine whether they met the inclusion criteria. Disagreements were resolved by discussion and consensus. Primary studies were included if they: (i) were published in a journal in full text (i.e., abstracts, letters, book chapters and dissertations were excluded); (ii) were published in English; (iii) evaluated an intervention for the prevention or treatment of anticipatory CINV; (iv) reported the proportion of patients experiencing complete control of anticipatory CINV and (v) the number of participants was >10 per study arm for comparative studies and >2 overall for non-comparative studies. Financial limitations precluded translation of guidelines published in languages other than English. The minimum number of required subjects in included pediatric studies was lower than that for adult studies in recognition of the smaller evidence base in pediatrics and the likelihood that pediatric studies would involve fewer patients than adult studies.
- b. **Prevalence of Anticipatory CINV Pre-post Use of 5-HT₃ Antagonists:** As several of the prominent adult-focused antiemetic guidelines recommend optimal control of acute CINV to prevent anticipatory CINV, a review of primary studies which evaluated the prevalence of anticipatory CINV in adult and pediatric patients was performed.
 - i. **Search Strategy:** The same set of citations identified by the search strategy for the prevention and treatment of anticipatory CINV systematic review was used, as a very broad search strategy was employed to identify anticipatory CINV studies. The search strategies are provided in Appendix C in the original guideline document.
 - ii. **Selection Criteria and Appraisal:** Citations were independently screened for relevancy by two reviewers. All citations identified as potentially relevant by either reviewer were included for full-text screening. Two reviewers independently evaluated the full-text

papers to determine whether they met the inclusion criteria. Disagreements were resolved by discussion and consensus. Studies were included if they were: (i) primary studies that were published in a journal in full text (i.e., abstracts, letters, book chapters and dissertations were excluded); (ii) published in English; (iii) determined the proportion of patients experiencing anticipatory CINV; (iv) the sample size per study arm was ≥ 10 subjects for pediatric studies and ≥ 20 subjects for adult only or mixed adult/pediatric studies; and (v) the study inclusion criteria did not specifically select for patients with post-chemotherapy CINV.

Number of Source Documents

Identification and Appraisal of Existing Guidelines

Nine guidelines that were either developed for use in adults and/or for use in children met the inclusion criteria and were assessed using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument. None of the guidelines were selected for adaptation.

Systematic Reviews of Pediatric and Adult Primary Studies

- Interventions to prevention and/or treatment of anticipatory chemotherapy-induced nausea and vomiting (CINV): Eleven studies met the inclusion criteria
- Prevalence of anticipatory CINV pre-post use of 5-HT₃ antagonists: Fifty studies (reported in 58 papers) met the inclusion criteria

See Appendix B in the original guideline document for a flowchart that outlines the search strategy for existing guidelines and Appendix C for a flowchart that outlines the search strategy for the systematic review.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

High Quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate Quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low Quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low Quality	Any estimate of effect is very uncertain

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Appraisal of Existing Guidelines

Each guideline identified through the search was independently reviewed and scored by at least two members of the Pediatric Oncology Group of Ontario (POGO) CINV Guideline Development Panel using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument. The domains assessed by this instrument include: scope and purpose; stakeholder involvement; rigor; clarity and presentation; applicability, and editorial independence. The domain scores and overall assessments of each reviewer were aggregated and presented for discussion at a panel meeting held by teleconference. The Rigor of Development quality domain score was emphasized. The AGREE scores are presented in Appendix B in the original guideline document. The suitability of each guideline for adaptation using the ADAPTE process was discussed by the panel.

Systematic Reviews of Primary Studies

Evidence summary tables of included studies were compiled and reviewed by two panel members before consideration by the panel.

The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system developed by Guyatt et al. (see the "Rating Scheme for the Strength of the Evidence" field) by one author and confirmed through discussion by the remaining panel members.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Health Questions

The guideline sought to answer the following health questions:

1. What approaches are recommended to prevent the development of anticipatory chemotherapy-induced nausea and vomiting (CINV) in children?
2. What interventions are recommended to control anticipatory CINV in children who develop it?

Guideline Development Panel

The Pediatric Oncology Group of Ontario (POGO) identified CINV as a key supportive care initiative in 2008 and the POGO CINV Guideline Development Group was formed in December 2008. Members were selected with a view to obtain inter-disciplinary representation from several POGO institutions as well as content expertise. Experts who had published in the area of CINV in children or who had a current research interest in CINV or supportive care in cancer were invited to join the guideline development group. After the completion of the first two POGO guidelines in the CINV series, panel members were asked to confirm their willingness to continue as members of the panel tasked with development of the third guideline in this series. Two members resigned and two new members were recruited.

Decision-making Process for Formulation of the Recommendations

Decisions were taken through panel discussions and any differences in opinion were resolved by consensus. The quality of evidence and strength of recommendations were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system developed by Guyatt et al. by one author and confirmed through discussion by the remaining panel members. If consensus was unable to be reached on any matter, a decision was made by the majority of panel members by a vote.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong Recommendation	When using Grading of Recommendations Assessment, Development and Evaluation (GRADE), panels make strong recommendations when they are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
Weak Recommendation	Weak recommendations indicate that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

External Review and Consultation Process

Who Was Asked to Review the Guideline?

Content Expert Review

Physicians, nurses and pharmacists with an active clinical and/or research interest in chemotherapy-induced nausea and vomiting (CINV) were asked to review the draft guideline.

External Stakeholder Review

Health care providers working at the Pediatric Oncology Group of Ontario (POGO) tertiary centres and their satellites and members of the POGO Supportive Care Steering Committee were asked to review the draft guideline and complete an online survey. Stakeholders from all 5 tertiary centres and 6 of the 7 satellite centres provided feedback. A total of 25 stakeholders provided survey responses.

What Process Was Followed?

The willingness of potential content expert reviewers to review the guideline was determined by contacting them by telephone or e-mail. Once agreement was obtained, the draft guideline was sent electronically along with instructions for the reviewer to complete a survey (see Appendix H in the original guideline document).

Following the content expert review, the draft guideline was sent electronically to health care providers who practice in POGO satellites and tertiary centres together with a request to review the document using a survey (see Appendix I in the original guideline document). Reviewers returned the completed the online survey.

Discussion of Feedback

The survey results were discussed in detail by the POGO CINV Guideline Development Panel and a decision on each point was taken by consensus. When the decision of the panel was not unanimous, a revision was made if it was supported by at least 60% of the guideline development panel members. The comments of the expert reviewers led to revisions to the guideline as outlined in Table 3 in the original guideline document and a summary of the expert reviewers' responses to the survey questions is provided in Table 4 in the original guideline document.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Optimizing the control of anticipatory chemotherapy-induced nausea and vomiting (CINV) in children receiving chemotherapy

Potential Harms

Few adverse effects were attributed to lorazepam; mild sedation occurred in 76% of the treatments where lorazepam was given and 32% of the control treatments. The recommended initial lorazepam dose was based on current pediatric dosing recommendations with the usual adult dose as

the maximum dose. This dose should be titrated to the needs of each child. For example, if this dose is associated with an unacceptable degree of sedation, lower doses are recommended for subsequent chemotherapy blocks.

Qualifying Statements

Qualifying Statements

The Pediatric Oncology Group of Ontario (POGO) Guideline for the Prevention and Treatment of Anticipatory Nausea and Vomiting due to Chemotherapy in Pediatric Cancer Patients was developed by health care professionals using evidence-based or best practice references available at the time of its creation. The content of the guideline will change since it will be reviewed and revised on a periodic basis. Care has been taken to ensure accuracy of the information. However, every health care professional using this guideline is responsible for providing care according to their best professional judgement and the policies and standards in place at their own institution.

Implementation of the Guideline

Description of Implementation Strategy

Guideline Implementation Considerations

Evidence-based guidelines should be used to select anti-emetic interventions to prevent acute and delayed chemotherapy-induced nausea and vomiting (CINV) for the initial chemotherapy. The child's response, as well as evidence-based recommendations, should be used to select antiemetic interventions to prevent acute and delayed CINV for subsequent chemotherapy.

Institutions should evaluate evidence-based guidelines for endorsement or adaptation and should consider developing antiemetic selection order sets or the incorporation of optimal antiemetic prophylaxis into cancer therapy order sets to facilitate their clinical use.

Health care providers should carefully and frequently evaluate CINV severity across all phases (anticipatory, acute and delayed) in children receiving chemotherapy. Particular attention should be paid to determining the incidence of CINV that may occur when the child is not in the inpatient or clinic setting and its severity. These assessments are needed to guide the need for treatment of anticipatory CINV, when present, and the selection of antiemetic prophylaxis for subsequent chemotherapy treatments. Attentive response to the child's overall CINV experience on the part of health care providers will likely minimize the development of anticipatory CINV.

Members of the health care team who have expertise in the provision of the recommended non-pharmacological interventions (hypnosis, systematic desensitization) should be identified and engaged in the care of children with anticipatory CINV.

Tools for Application

Meticulous attention to the overall CINV experience (anticipatory, acute and delayed phase) of children receiving chemotherapy is required. Validated screening and assessment tools must be developed to facilitate timely and efficient identification of children who do not experience complete CINV control despite receiving guideline-informed antiemetic prophylaxis. CINV diaries (paper or electronic) should be considered to record and track the experience of patients.

Organizational Barriers and Cost Implications

Routine systematic screening of all patients about to receive chemotherapy regarding their experience of anticipatory CINV is critical to the identification of patients who warrant intervention. Each organization should ensure that clinicians accept this as a standard of care and that they have the resources to perform this screening and provide appropriate interventions.

The availability of the resources required to implement the recommendations may be limited at many institutions. Since appropriately trained staff is the primary resource required for the incorporation of non-pharmaceutical interventions to control anticipatory CINV, it is suggested that each institution review the number of available child life specialists, psychologists and nurses with the relevant expertise to deliver these therapies.

Costs related to antiemetic agents, especially those used for acute and delayed phase CINV control, may increase when evidence-based guideline recommendations are followed. These increased costs may be counter-balanced by decreased costs due to improved CINV control.

Key Review Criteria for Monitoring and/or Audit Purposes

Routine monitoring and tracking of patients' level of overall CINV control (anticipatory, acute and delayed phase) would not only provide a means to respond to the needs of individual patients but would also provide very much needed information regarding the emetogenicity of chemotherapy regimens in children.

Periodic audits of adherence of antiemetic prescribing to the guideline should be performed at individual institutions. Ideally, each prescriber should receive feed-back regarding the extent of their adherence to the guideline and the rate of complete anticipatory, acute and delayed CINV control seen in their patients.

Implementation Tools

Audit Criteria/Indicators

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Dupuis LL, Robinson PD, Boodhan S, Holdsworth M, Portwine C, Gibson P, Phillips R, Maan C, Stefin N, Sung L. Guideline for the prevention and treatment of anticipatory nausea and vomiting due to chemotherapy in pediatric cancer patients. Toronto (ON): Pediatric Oncology Group of Ontario (POGO); 2014 Apr 23. 57 p. [99 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Apr 23

Guideline Developer(s)

Pediatric Oncology Group of Ontario - Professional Association

Source(s) of Funding

Pediatric Oncology Group of Ontario (POGO)

Ministry of Health and Long Term Care, Ontario

L. Sung and L.L. Dupuis received partial salary support from the Children's Oncology Group

Guideline Committee

Pediatric Oncology Group of Ontario (POGO) CINV Guideline Development Panel

Composition of Group That Authored the Guideline

Panel Members: L. Lee Dupuis, pediatric oncology pharmacist (*Chair*); Sabrina Boodhan, pediatric pharmacist; Paul Gibson, pediatric hematologist/oncologist; Mark Holdsworth, pediatric oncology pharmacist; Bob Phillips, pediatric hematologist/oncologist; Carol Portwine, pediatric hematologist/oncologist; Paula Robinson, guideline methodologist; Lillian Sung, pediatric hematologist/oncologist

Financial Disclosures/Conflicts of Interest

The guideline development panel members had no conflicts of interest with respect to the development of this guideline. All work produced by the Pediatric Oncology Group of Ontario (POGO) CINV Guideline Development Panel is editorially independent of its funding agencies.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the [Pediatric Oncology Group of Ontario \(POGO\) Web site](#) .

Print copies: Available through the POGO office, 480 University Avenue, Suite 1014, Toronto, ON, CANADA; M5G 1V2 Phone: 416-592-1232; Toll free: 1-855-FOR-POGO (367-7646).

Availability of Companion Documents

The following is available:

- Dupuis LL, Robinson PD, Boodhan S, Holdsworth M, Portwine C, Gibson P, Phillips R, Maan C, Stefin N, and Sung L. Guideline for the prevention and treatment of anticipatory nausea and vomiting due to chemotherapy in pediatric cancer patients. *Pediatr Blood Cancer*. 2014 Aug;61(8):1506-12. Electronic copies: Available for purchase from the [Pediatric Blood and Cancer Web site](#) .

In addition, a suggested criterion for monitoring and/or audit purposes is included in the [original guideline document](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on March 10, 2015. The information was verified by the guideline developer on April 9, 2015. This summary was updated by ECRI Institute on October 21, 2016 following the U.S. Food and Drug Administration advisory on opioid pain and cough medicines combined with benzodiazepines. This summary was updated by ECRI Institute on February 15, 2017 following the U.S. Food and Drug Administration advisory on general anesthetic and sedation drugs.

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